SYNTHESIS OF BRIDGEHEAD-NITROGEN HETEROCYCLES FROM PYRYLIUM SALTS:
[1,2,4]TRIAZINE RING SYSTEM

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Abstract- A number of thiazolo[2,3-c]pyrido[2,1-f][1,2,4]triazine derivatives have been prepared by reaction of the 4-oxo-6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium-2-thiolate, available from 2-ethoxycarbonyl-4,6-diphenylpyrylium cation and thiosemicarbazide, with phenacyl bromides and subsequent cyclization by the action of acetic anhydride.

In the last few years we were involved in a program aiming to develop synthetic approaches for nitrogen-bridgehead heterocycles utilizing readily available 2-functionalized pyrylium cations as starting materials. In this context, we have reported the reaction of 2-ethoxycarbonyl-4,6-diphenylpyrylium tetrafluoroborate (1) with unsubstituted and N3-arylamidrazones to give 4-oxidopyrido[2,1-f][1,2,4] triazinium betaines and 4-oxo-3,4-dihydropyrido[2,1-f][1,2,4]triazinium salts respectively1. Similarly, we have found that compound (1) reacts with thiocarbonohydrazide and carbonohydrazide to give the cross-conjugated betaines 3-amino-4-oxo-6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium-2-thiolate2 and 3-amino-4-oxo-6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium-2-olate3 repectively. On the other hand, compound (1), reacts with hydrazides to give the corresponding N-amido pyridinium salts which by the action of hydrazine undergo cyclization to give 2-substituted 3-amino-4-oxo-6,8-diphenyl-3,4-dihydropyrido-[2,1-f][1,2,4]triazin-9-ium salts4.

We now describe a general method for the preparation of some derivatives of the unknown thiazolo[2,3-c]pyrido[2,1-f][1,2,4]triazine ring system from 2-ethoxycarbonyl-4,6-diphenylpyrylium cation (1) by sequential treatment with thiosemicarbazide, phenacyl bromides and cyclohydration by the action of acetic anhydride. The pyrylium salt (1), readily available from ethyl pyruvate, benzylidenacetophenone and boron trifluoride diethyl ether5, reacts with thiosemicarbazide in methanol at reflux temperature for 8 h to give 4-oxo-6,8-diphenyl-3,4-dihydropyri-
do[2,1-f][1,2,4]triazin-9-ium-2-thiolate (2) as a crystalline solid in 43% yield. Compound (2) undergoes S-alkylation by the action of phenacyl bromides to give the corresponding 4-oxo-2-phenacylthio-6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium bromides (3), which by treatment with perchloric acid in ethanol at reflux temperature are converted into the corresponding perchlorates (4) in almost quantitative yields (Table 1). Similarly, compound (2) reacts with trimethyloxonium tetrafluoroborate to give the S-methyl derivative (5) in high yield. Compounds (4) undergo cyclization by the action of acetic anhydride to give the corresponding 3-aryl-5-oxo-7,9-diphenylthiazolo[2,3-c]pyrido[2,1-f][1,2,4]triazin-10-ium perchlorates (6) as crystalline solids in high yields (Table 2).
On the other hand, when ethanolic solutions of compounds (4) are treated with equimolecular amount of triethylamine, betaines (7) are isolated as crystalline solids in high yields. Methylation of compounds (7) with trimethyloxonium tetrafluoroborate leads exclusively to 3-methyl-4-oxo-2-phenacylthio-6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium tetrafluoroborates (8) in high yields, because of the availability of the lone pair at N-1 position is strongly decreased by influence of the positive charge on the neighbouring bridgehead nitrogen atom.

Structural elucidation of (2)-(8) is accomplished on the basis of spectral and microanalytical data. The ir spectra of (2), (3), (4), (5), (6) and (8) show a strong absorption band in the region 1690-1738 cm\(^{-1}\), attributable to the carbonyl group in the triazinone moiety, while the presence of another different carbonyl group in compounds (3), (4), (7) and (8) is confirmed by the absorption band in the region 1664-1693 cm\(^{-1}\). In the \(^{1}\)H-nmr spectra of (3), (4), (7) and (8) the chemical shift of the methylene group (S-CH\(_2\)-COAr) is characteristic at \(\delta\) 4.6 ppm, while in the \(^{1}\)H-nmr spectra of compounds (6) this signal is absent, although a new signal corresponding to the proton at 2 position appears at \(\delta\) 7.1 ppm as a singlet.

**EXPERIMENTAL**

Melting points were obtained on a Kofler hot-stage apparatus and are uncorrected. Ir spectra were run using NaCl plates on a Nicolet FT-5DX spectrophotometer in Nujol emulsions. \(^{1}\)H-nmr spectra were obtained on a Varian EM-360 A spectrometer at 60 MHz. Mass spectra were recorded on a Hewlett-Packard 5993 C spectrometer. Elemental analyses were performed with a Perkin Elmer 240 instrument.

**Preparation of 4-Oxo-6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium-2-thiolate 2.** To a solution of 2-ethoxycarbonyl-4,6-diphenylpyrylium tetrafluoroborate (0.39 g, 1 mmol) in methanol (20 ml), thiosemicarbazide (0.092 g, 1 mmol) was added. The reaction mixture was stirred at reflux temperature for 8 h. After cooling, the precipitated solid was separated by filtration and recrystallised from chloroform to give 2 (0.14 g, 43%) as orange prisms; mp 186-187°C (Found: C, 68.72; H, 4.08; N, 12.55. \(\text{C}_{19}\text{H}_{13}\text{N}_{3}\text{OS}\) requires C, 68.86; H, 3.95; N, 12.68 %); \(\nu_{\text{max}}\) (Nujol) 1690, 1625, 1490, 1400, 1330, 1260, 1210, 1150, 1030, 1000, 985, 910, 885, 770, 700; \(\delta\) (DMSO-\(d_6\)) 8.90 (1H,d,\(J=2\)Hz), 8.70 (1H,d,\(J=2\)Hz), 8.65-7.15 (11H,m); m/z (%) 331 (M\(^+\), 14), 299 (29), 270 (7), 258 (13), 230 (91), 191 (44), 64 (100).

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TABLE 1. Preparation of 4-Oxo-2-phenacylthio-6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium Perchlorates 4.

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<th>Mp(°C)</th>
<th>Yield (%)</th>
<th>Found C</th>
<th>Found H</th>
<th>Found N</th>
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<th>Required H</th>
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General Procedure for the Formation of 4-Oxo-2-phenacylthio-6,8-diphenyl-3,4-di-
hydropyrido[2,1-f][1,2,4]triazin-9-ium Perchlorates 4. To a solution of 4-oxo-
6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium-2-thiolate 2 (0.5 g, 
1.5 mmol) in absolute ethanol (20 ml), an equimolecular amount of the 
appropriate phenacyl bromide was added. The reaction mixture was stirred at 
reflux temperature for 8 h. After cooling, the precipitated solid was separated 
by filtration, dried and recrystallised from ethanol to give 3. To a suspension of 
3 (1 mmol) in ethanol (15 ml), 70% perchloric acid (2 ml) was added. The 
mixture was kept under reflux temperature for 2 h, and the resulting 
precipitated solid was filtered off and recrystallised from ethanol to give 4 
(see Table 1).

Preparation of 2-Methylthio-4-oxo-6,8-diphenyl-3,4-dihydropyrido[2,1-f]
triazin-9-ium Tetrafluoroborate 5. 4-Oxo-6,8-diphenyl-3,4-dihydropyrido[2,1-f] 
[1,2,4]triazin-9-ium-2-thiolate 2 (0.331 g, 1 mmol), trimethyloxonium tetrafluor-
borate (0.148 g, 1 mmol) and dry dichloromethane (10 ml) were stirred under 
reflux temperature for 4 h. After cooling, the white precipitated solid was 
separated by filtration, dried and recrystallised from ethanol to give 5 (0.38 
g, 88%) as colourless prisms; mp 236-237°C (Found: C, 55.31; H, 3.89; N, 9.92. 
C_{20}H_{16}BF_{4}N_{3}OS requires C, 55.45; H, 3.72; N, 9.70 %; ν_{max} (Nujol) 3165, 1738, 
1630, 1596, 1557, 1404, 1376, 1359, 1280, 1265, 1213, 1060, 904, 769, 717, 698 
cm^{-1}; δ (CDCl_{3}/TFA) 9.05 (1H,d,J=2Hz), 8.40 (1H,d,J=2Hz), 8.1-7.5 (10H,m), 
2.3 (3H,s); m/z (%) 346 (M^{+}-BF_{4}^{-},13), 345 (M^{+}-HBF_{4}^{-},54), 299 (23), 298 (100), 258 
(3), 231 (23), 230 (65), 77 (32).

General Procedure for the Formation of 3-Aryl-5-oxo-7,9-diphenylthiazolo[2,3-c]
pyrido[2,1-f][1,2,4]triazin-10-ium Perchlorates 6. A solution of the appropriate 
4-oxo-2-phenacylthio-6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium 
perchlorate 4 (2 mmol) in acetic anhydride (15 ml) was heated under reflux 
temperature for 1 h. After cooling, diethyl ether (30 ml) was added and the 
separated solid was collected by filtration, washed with diethyl ether (2x5 ml), 
dried and recrystallised from ethanol to give 6 (see Table 2 and 3).

General Procedure for the Formation of 2-Phenacylthio-6,8-diphenylpyrido[2,1-f] 
[1,2,4]triazin-9-ium-4-olate 7. To a suspension of the appropriate 4-oxo-2-phen-
acylthio-6,8-diphenyl-3,4-dihydropyrido[2,1-f][1,2,4]triazin-9-ium perchlorate 
4 (2 mmol) in ethanol (30 ml), an equimolecular amount of triethylamine was 
added. The resulting mixture was stirred at room temperature for 4 h. The solid 
was filtered off, dried and recrystallised from ethanol to give 7.

7a, Ar=C_{6}H_{5} (0.74 g, 86%) as white prisms; mp 197-200°C (Found: C, 72.28; H, 
4.13; N, 9.51. C_{27}H_{19}N_{3}O_{2}S requires C, 72.14; H, 4.26; N, 9.35 %; ν_{max} (Nujol) 
1676, 1639, 1608, 1577, 1473, 1437, 1364, 1322, 1291, 1218, 1192, 1161, 1146, 
1000, 979, 902, 792, 762, 755, 722, 697, 686, 642; δ (CDCl_{3}/TFA) 9.05 (1H,d, 
J=2Hz), 8.5 (1H,d,J=2Hz), 8.05-7.30 (15H,m), 4.60 (2H,s).
7b, Ar=4-H$_3$COC$_6$H$_4$ (0.8 g, 83%), as white prisms; mp 213-214°C (Found: C, 69.02; H, 4.31; N, 8.66. C$_{18}$H$_{14}$N$_2$O$_2$S requires C, 70.13; H, 4.41; N, 8.76%). $\nu_{\text{max}}$ (Nujol) 1693, 1636, 1612, 1599, 1510, 1473, 1456, 1435, 1400, 1359, 1323, 1263, 1207, 1168, 1032, 979, 827, 767, 723, 702, 690 cm$^{-1}$; $\delta$(CDCl$_3$) 9.05 (1H,d,J=2Hz), 8.50 (1H,d,J=2Hz), 8.10-6.90 (14H,m), 4.50 (2H,s), 4.10 (3H,s).

7c, Ar=4-ClC$_6$H$_4$ (0.92 g, 96%), as white prisms; mp 229-230°C (Found: C, 66.91; H, 3.62; N, 8.75. C$_{27}$H$_{18}$CIN$_3$O$_2$S requires C, 67.01; H, 3.75; N, 8.68%). $\nu_{\text{max}}$ (Nujol) 1698, 1642, 1613, 1591, 1473, 1446, 1435, 1402, 1356, 1317, 1290, 1199, 1165, 1091, 979, 855, 790, 769, 725, 704, 694 cm$^{-1}$; $\delta$(CDCl$_3$/TFA) 9.15 (1H,d,J=2Hz), 8.50 (1H,d,J=2Hz), 8.20-7.30 (14H,m), 4.60 (2H,s).

### TABLE 3. Spectral Data of Compounds 4 and 5.

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<td>9.10 (1H, d, J=2Hz), 8.40 (1H, d, J=2Hz), 8.10-7.20 (15H, m), 4.60 (2H, s).</td>
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<td>3160, 1721, 1647, 1625, 1596, 1570, 1510, 1313, 1261, 1203, 1174, 1095, 1022, 985, 896, 841, 785, 769, 700, 688, 623.</td>
<td>9.05 (1H, d, J=2Hz), 8.40 (1H, d, J=2Hz), 8.1-6.9 (14H, m), 4.60 (2H, s), 4.0 (3H, s).</td>
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<td>9.10 (1H, d, J=2Hz), 8.45 (1H, d, J=2Hz), 8.1-7.4 (15H, m), 7.10 (1H, s).</td>
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**General Procedure for the Formation of 3-Methyl-4-oxo-2-phenacythio-6,8-diphenyl-1,3-dihydropyrido[2,1-f][1,2,4]triazin-9-ium Tetrafluoroborates 8.** To a suspension of the appropriate betaine 7 (1 mmol) in dry dichloromethane (15 ml), trimethylxonium tetrafluoroborate (0.148 g, 1 mmol) was added. The reaction mixture was stirred at reflux temperature for 3 h. On cooling, the resulting precipitated solid was filtered off and recrystallised from ethanol to give 8.

**8a, Ar=4-H₃COCH₆H₄ (0.52 g, 90%) as yellow prisms:** mp 207-209°C (Found: C, 59.68; H, 4.25; N, 7.16. C₂₉H₂₄BF₄N₃O₃S requires C, 59.91; H, 4.16; N, 7.23%). ν max (Nujol) 1721, 1664, 1625, 1596, 1534, 1347, 1262, 1206, 1177, 1060, 900, 832, 764, 721, 707; ν max (CDCl₃/TFA) 9.10 (1H, d, J=2Hz), 8.40 (1H, d, J=2Hz), 8.1-6.99 (14H, m), 4.60 (2H, s), 4.0 (3H, s), 3.80 (3H, s); m/z (%) 494 (M⁺-BF₄⁻), 493 (1), 313 (7), 299 (23), 298 (90), 231 (24), 230 (52), 152 (8), 151 (4), 139 (100), 107 (19), 77 (42).
8b, Ar=4-ClC₆H₄ (0.55 g, 93%), as white prisms; mp 211-213°C (Found: C, 57.38%; H, 3.73%; N, 7.28. C₂₈H₂₁BClF₄N₂O₂S requires C, 57.41%; H, 3.61%; N, 7.17%). max (Nujol) 1728, 1685, 1589, 1435, 1290, 1215, 1195, 1060, 898, 854, 812, 765, 723, 702, 682; (CDCl₃/TFA) 11.40 (1H, d, J=2Hz), 8.40 (1H, d, J=2Hz), 8.10-7.20 (14H, m), 4.60 (2H, s), 3.80 (3H, s); m/z (%): 500 (M⁺-BF₄⁻, 1), 498 (3), 313 (5), 299 (4), 298 (84), 231 (25), 230 (38), 156 (3), 155 (4), 154 (8), 153 (6), 141 (29), 139 (100), 113 (6), 111 (15), 77 (20).

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